

Claims:

What is claimed is:

1. A method for identifying a target site on a human AATYK polypeptide which may be suitable for therapeutic intervention, comprising identifying as target sites
5 those amino acid changes in the human AATYK polypeptide that correspond to evolutionarily significant nucleotide changes identified according to the method comprising:
 - a. comparing the human polynucleotide sequence that encodes human AATYK with a corresponding non-human primate polynucleotide sequence to identify
10 any nucleotide changes; and
 - b. determining whether said human nucleotide changes are evolutionarily significant.
2. The method of claim 1 wherein the non-human primate is a chimpanzee or a gorilla.
- 15 3. A method for identifying a target site on a human AATYK polynucleotide which may be suitable for therapeutic intervention, comprising identifying as target sites nucleotide changes in the human AATYK polynucleotide that are evolutionarily significant nucleotide changes identified according to the method comprising:
 - a. comparing the human polynucleotide sequence with the
20 corresponding non-human primate polynucleotide sequence to identify any nucleotide changes; and
 - b. determining whether said human nucleotide changes are evolutionarily significant.
4. The method of claim 3 wherein the non-human primate is a chimpanzee or a
25 gorilla.
5. A method of identifying an agent which may modulate a physiological trait, said method comprising contacting at least one agent to be tested with a polypeptide

encoded by an evolutionarily significant human AATYK polynucleotide sequence, or a composition comprising said polypeptide, wherein an agent is identified by its ability to modulate function of the human polypeptide sequence.

6. The method of Claim 5, wherein the polypeptide encoded by an evolutionarily significant human AATYK polynucleotide sequence is a polypeptide encoded by a polynucleotide sequence selected from the group consisting of nucleotides 2180-2329 of SEQ ID NO:14, nucleotides 2978-3478 of SEQ ID NO:14, and nucleotides 3380-3988 of SEQ ID NO:14.

7. A method of identifying an agent which may modulate a physiological trait, said method comprising contacting at least one agent to be tested with a polynucleotide encoding an evolutionarily significant human AATYK protein, or a composition comprising said polynucleotide, wherein an agent is identified by its ability to modulate function of the human polynucleotide sequence.

8. The method of Claim 7, wherein the polynucleotide is selected from the group consisting of nucleotides 2180-2329 of SEQ ID NO:14, nucleotides 2978-3478 of SEQ ID NO:14, and nucleotides 3380-3988 of SEQ ID NO:14.

9. A method for correlating an evolutionarily significant nucleotide change in the human AATYK gene to a physiological condition in a human, comprising:
analyzing a functional effect, if any, of an AATYK polynucleotide containing the evolutionarily significant nucleotide change in a suitable model system, wherein presence of a functional effect indicates a correlation between the evolutionarily significant nucleotide change and the physiological condition.

10. The method of claim 9, wherein the polynucleotide sequence is selected from the group consisting of nucleotides 2180-2329 of SEQ ID NO:14, nucleotides 2978-3478 of SEQ ID NO:14, and nucleotides 3380-3988 of SEQ ID NO:14.

11. A method for correlating an evolutionarily significant nucleotide change in

the human AATYK gene a to a physiological condition in a human, comprising:

- analyzing a functional effect, if any, of a polypeptide encoded by an AATYK polynucleotide sequence containing an evolutionarily significant nucleotide change in a suitable model system, wherein presence of a functional effect indicates a correlation
5 between the evolutionarily significant nucleotide change and the physiological condition.

12. The method of claim 11, wherein the polynucleotide sequence is selected from the group consisting of nucleotides 2180-2329 of SEQ ID NO:14, nucleotides 2978-3478 of SEQ ID NO:14, and nucleotides 3380-3988 of SEQ ID NO:14.

13. An isolated nucleotide sequence selected from the group consisting of:
10 a) a nucleotide sequence selected from the group consisting of nucleotides 2180-2329 of SEQ ID NO:14, nucleotides 2978-3478 of SEQ ID NO:14, and nucleotides 3380-3988 of SEQ ID NO:14; and
b) an isolated nucleotide sequence having at least 85% homology to a nucleotide sequence of a).

- 15 14. An isolated polypeptide selected from the group consisting of:
a) a polypeptide encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO:17 and SEQ ID NO:18; wherein said encoding is based on the open reading frame of SEQ ID NO:14; and
b) a polypeptide encoded by a nucleotide sequence having at least 85%
20 homology to a nucleotide sequence selected from the group consisting of SEQ ID NO:17 and SEQ ID NO:18; wherein said encoding is based on the open reading frame of SEQ ID NO:14.

15. An isolated polypeptide selected from the group consisting of:
a) a polypeptide encoded by a nucleotide sequence selected from the group
25 consisting of nucleotides, 1-150 of SEQ ID NO:17, nucleotides 202-351 of SEQ ID NO:17, nucleotides 799-948 of SEQ ID NO:17, nucleotides 901-1050 of SEQ ID NO:17, nucleotides 799-1299 of SEQ ID NO:17, and nucleotides 1201-1809 of SEQ ID NO:17;

wherein said encoding is based on the open reading frame of SEQ ID NO:14; and

b) a polypeptide encoded by a nucleotide sequence having at least 85% homology to a nucleotide sequence of a).

16. An isolated polypeptide selected from the group consisting of:

5 a) a polypeptide encoded by a nucleotide sequence selected from the group consisting of nucleotides 799-1299 of SEQ ID NO:18, and nucleotides 1201-1809 of SEQ ID NO:18; wherein said encoding is based on the open reading frame of SEQ ID NO:14; and

10 b) a polypeptide encoded by a nucleotide sequence having at least 85% homology to a nucleotide sequence of a).

17. An isolated polynucleotide comprising SEQ ID NO: 17, wherein the coding capacity of the nucleic acid molecule is based on the open reading frame SEQ ID NO:14.

18. The isolated polynucleotide of Claim 17, wherein said polynucleotide is a *Pan troglodytes* polynucleotide.

15 19. An isolated polynucleotide comprising SEQ ID NO: 18, wherein the coding capacity of the nucleic acid molecule is based on the open reading frame of SEQ ID NO:14.

20. The isolated polynucleotide of Claim 19, wherein said polynucleotide is a *Gorilla gorilla* polynucleotide.

20 21. A method of determining whether a human polynucleotide sequence which has been associated with brain development in humans has undergone evolutionarily significant change relative to a non-human primate, comprising:

a. comparing the human polynucleotide sequence with the corresponding non-human primate polynucleotide sequence to identify any nucleotide changes; and
25 b. determining whether said human nucleotide changes are evolutionarily significant.

22. The method of claim 21, wherein the polynucleotide encodes a human AATYK polypeptide.

5 23. The method of claim 21, wherein the polynucleotide is about 150 to 600 bases in length.

24. The method of claim 21, wherein the non-human primate is selected from the group consisting of chimp and gorilla.

10

25. The method of claim 21, wherein the evolutionary significance of the nucleotide change is determined by the ratio of the non-synonymous substitution rate (K_A) to the synonymous rate (K_S) of the nucleotide sequence.

15 26. The method of claim 25, wherein the K_A/K_S ratio is selected from the group consisting of at least 0.75, at least 1.00, at least 1.25, at least 1.50, and at least 2.00.